

REMARKS

Claims 1, 2, 7-12, 14-24 and 27-41 are currently pending in the present application. No amendment has been made in the current response. Claims 1 and 27 are the only pending independent claims.

All previous rejections have been withdrawn. The Examiner has rejected claims 1, 2, 7-12, 14-24 and 27-41 on new ground, i.e., as being unpatentable under 35 U.S.C. § 103(a) over the combined disclosures of U.S. Patent No. 4,855,326 ("the '326 patent") in view of U.S. Patent No. 6,099,863 ("the '863 patent") and further in view of U.S. Patent No. 5,904,929 ("the '929 patent"). The '326 patent is newly cited in the pending Office Action, and the '863 and '929 patents have been cited previously.

The Examiner states that "it would have been obvious to include the galanthamine salt of the '863 patent into the *thin oral sheets of the '326 patent since the '326 reference is suggestive of cholinesterase inhibitors* and discloses fast dissolving oral dosage forms." The Examiner continues that the "combination would have been obvious following the suggestions of the '326 application [*sic, patent*] and teachings of the '863 *to quickly deliver the compounds orally.*" [emphasis added in italics]

Applicants respectfully submit that claims 1 and 27 and their dependent claims are not *prima facie* obvious in view of the combination of the '326, '863 and '929 patents, at least because the cited prior art did not teach to use a film-shaped medicament for buccal administration of galanthamine, salts or derivatives thereof, with the dissolution profile recited in the present claims, i.e., within thirty minutes after buccal administration of the medicament, the medicament releases such an amount of the cholinergic active substance(s) contained therein to the oral cavity that an effective plasma level is achieved.

The '326 patent discloses a spun fibrous pharmaceutical composition comprising a mass of spun fibers and a medicament distributed on or incorporated in said fibrous mass, the spun fibers are made of a readily water-soluble sugar material (col. 2, lines 35- 40, claim 26). The reference emphasizes that "it is important that the final dosage form retains its fibrous character so that it will dissolve rapidly in the saliva of the mouth or other solvent" (col. 5, lines 60-63). The reference describes that, preferably, the fiber "material is compacted as much as possible to

produce a wafer-like structure while avoiding fracturing of the fibers or loss of the discrete fibrous identity" (col. 5, line 67 to col. 6, line2).

It is readily apparent to those skill in the art that this wafer-like structure is very different from the film-shaped medicament recited in the present claims. The presently claimed film-shaped medicament comprises at least one layer that contains the active ingredient and does not require any fibrous character. In addition, unlike the film-shaped medicament recited in claim 1 and its dependent claims, the wafer-like structure in the '326 patent is mucoadhesive, because it mainly consists of sugars, such as sucrose, fructose, dextrose, mannitol, sorbitol and the like, which are commonly known to tend to stick on the skin, including the mucous membrane.

In addition, contrary to the Examiner's belief, the '326 patent does NOT teach *thin oral sheets*. It describes that for use in topical transdermal delivery of a medicament, the spun fibrous product can be compressed into thin sheets for production of wafers that can be combined with adhesive strips to produce bandage strips or patches (col. 10, lines 19-23). Nowhere does the '326 patent describe to use the compressed thin sheets of spun fibrous product for oral or buccal administration of any drug. Indeed, in view of the very fragile nature of spun sugar and the importance to remain the fibrous character, one skilled in the art would not have been motivated to use the compressed thin sheets of spun sugar for production of any dosage form that does not have a supporting mechanism, such as the adhesive strips in bandage or patches. The Examiner states that the '326 patent discloses "sheets or wafer [that] comprises multiple layers including a foil backing layer (col. 6, lin. 65-col. 7, lin. 7)." However, the cited portion of the specification contains no disclosure on sheets or wafer, let alone thin sheets for oral administration. Rather, it merely describes to use a foil laminate material to encapsulate "the fiber product" in a foil laminate pouch.

Moreover, the '326 patent provides no specific motivation for one skilled in the art to use a rapid release formulation for buccal administration of galanthamine or salts or derivatives thereof. The '326 patent describes a list of actives, which include, in general term, antiparkinson (Table VI). Contrary to the Examiner's statement, *cholinesterase inhibitors* are not specifically suggested by the '326 patent. There are many drugs that can be used as antiparkinson (see, e.g., Wikipedia <http://en.wikipedia.org/wiki/Antiparkinson>). The '326 patent contains no teaching or suggestion for one to choose galanthamine out of the many potential antiparkinsons for delivery with its spun fibrous pharmaceutical composition.

The '863 patent does not compensate for the defects of the '326 patent. The '863 patent describes a fast-dissolving tablet for oral administration comprising galanthamine. The tablet has to be swallowed by a patient and delivers the active agent after being dissolved in the stomach. The *in-vitro* dissolution studies depicted in Example 6 cannot be used to support the view that the tablets dissolve in the oral cavity and begin to deliver their active payloads within five minutes. In those *in vitro* studies, the tablets were dissolved in a high excess of purified water at 37°C, a condition drastically different from that in the oral mucosa, where high amounts of water are not present. Thus, results from the *in-vitro* dissolution studies do not give any hint as to how fast the tablets dissolve in the oral cavity. In addition, nowhere does the '863 patent teach or suggest that its fast-dissolving tablet is for buccal administration. Thus, one would have no reason to keep the tablet in oral cavity for minutes before he swallows it down.

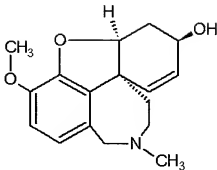
The presently claimed film-shaped medicament for buccal administration is completely different from the fast-dissolving tablet described in the '863 patent. The film-shaped medicament absorbs saliva and the active substance is released from the medicament into the oral cavity and absorbed via the oral mucosa. In the contact region of the application area, the active substance can be delivered directly from the medicament to the underlying mucosa. The presently claimed medicament leads to a quick onset of action during the application period, and has the advantage that it can be administered to a patient even when there is no liquid available or when the patient suffers from difficulty in swallowing.

Thus, the '863 patent, which discloses fast-dissolving tablets that dissolve quickly in the stomach, by no means, teaches or suggests to use the presently claimed film-shaped medicament to *quickly deliver the compounds orally* via buccal administration.

The '929 patent does not compensate for the defects of the '326 and '863 patents, because it also contains no teaching or suggestion on using a film-shaped medicament for rapid release buccal administration of galanthamine.

In addition, it is highly unpredictable whether galanthamine can be administered via buccal administration at all. Not all drugs are suitable for buccal administration for various reasons, e.g., chemical or physical properties of the drug, mechanism of action, side effect, etc. Those skilled in the art are aware of the fact that galanthamine is a molecule that has a relatively higher molecular weight (i.e. 287) compared to many other pharmaceutically active substances. Moreover, as shown below, galanthamine has an aminic structure that is either charged and/or

highly polar:



For a pharmaceutical substance to be effective via buccal administration, the active substance has to penetrate the buccal mucosa. However, at the time of filing the presently claimed invention, it was not clear at all, if and to which extent galanthamine might penetrate the buccal mucosa in view of the chemical or physical properties of the drug. Indeed, at the time of filing the presently claimed invention, there had been a number of administration forms for galanthamine, but none of which disclosed wafers for buccal administration of galanthamine.

Even assuming that one of ordinary skill in the art were motivated to try buccal administration of galanthamine, which Applicants strongly disagree, he would have been discouraged from using a rapid release film-shaped formulation as that recited in present claims, i.e., within thirty minutes after buccal administration of the medicament, the medicament releases such an amount of the cholinergic active substance(s) contained therein to the oral cavity that an effective plasma level is achieved. As discussed in the specification of the present application, side-effects were known to be associated with the administration of direct-release dosage forms of galanthamine, e.g., particularly in patients not previously treated with galanthamine, the high plasma concentration of galanthamine may lead to peripheral, especially gastrointestinal and cardiovascular, side effects (intestinal cramps, diarrhea, hypotension). See para. [0013]. A rapid release film-shaped formulation as that recited in the present claims would be expected to have a faster onset of action in the oral cavity than the tablets that deliver galanthamine to the gastrointestinal tract. An even higher plasma concentration galanthamine, thus more severe side-effects, would have been expected from the buccal administration of a rapid releasing film-shaped formulation for galanthamine. See para. [0019].

In view of the highly unpredictable nature of buccal administration of galanthamine and

the known side-effects associated with the direct release dosage forms of galanthamine, in the absence of specific teaching or suggestion from the '326, '863 and '929 patents discussed above, one of ordinary skill in the art would not have been motivated to incorporate galanthamine or any of its salts or derivatives into the compressed thin sheets of spun sugar of the '326 patent or any film dosage form for rapid release buccal administration as that recited in the present claims with a reasonable expectation of success.

Only through innovative experimentation, Applicants discovered for the first time that a film-shaped formulation for buccal administration of galanthamine affords rapid onset of action to achieve the effective plasma level, without the occurrence of unacceptable peripheral side effects. As discussed in detail in the specification, such superior result is completely unexpected. See e.g., para. [0019].

Accordingly, reconsideration and withdrawal of the rejection of claims 1-3, 7-9, 11, 12, 14-24 and 27-41 as being unpatentable over the combination of the '326, '863 and '929 patents are respectfully requested.

It is respectfully submitted that the present application, including claims 1, 2, 7-12, 14-24 and 27-41, is in condition for allowance and such action is respectfully solicited. Applicants appreciate the effort of the Examiner and look forward to receiving the Notice of Allowance of all pending claims.

Respectfully submitted,

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7/18/2011
(Date)

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